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EXAMINER	
LUCAS, ZACHARIAH	
ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/084,691	BUKH ET AL.	
	Examiner	Art Unit	
	Zachariah Lucas	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 December 2000*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-59* is/are pending in the application.

4a) Of the above claim(s) *1,3,6-10,17,18,20-31,45 and 47-58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,5,11-16,19,32-44,46 and 59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5-26-1998*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Currently, claims 1, and 3-59 are pending in the application.

2. The examiner to whom the case has been docketed in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Examiner Zachariah Lucas in Art Unit 1648.

Election/Restrictions

3. Applicant's election of Group II, and the sequences represented by SEQ ID NO: 206 in Paper No. 9 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

It is noted that the Restriction Requirement required the election of a species identified by a specific core protein, universal peptide, or genotype specific peptide. The species election requirement is hereby withdrawn to the extent that peptides of the elected core protein are treated as distinct species from the core protein. Thus, the elected species comprise the core protein of SEQ ID NO: 206, and peptides thereof.

4. Claims 1, 3, 6-10, 17, 18, 20-31, 45, and 47-58 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions or species, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 9.

Information Disclosure Statement

5. The information disclosure statement (IDS) submitted on May 26, 1998, is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner.

The following references are in a foreign language accompanied by an English abstract. Due to this, the references have been examined only to the extent of the disclosure in the abstract.

WO 92/21759 (Brechot et al.)
JP 5068562 (Shuichi et al)

Priority

Applicant's claim for domestic priority under 35 U.S.C. 120 to U.S. application 08/086,428 is acknowledged. However, the application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for the inventions relating to the HCV core proteins and peptides of this application. The teachings of the prior application are limited to those concerned with the sequences and peptides of the HCV E1 proteins, and provide no basis for support to the core proteins and peptides claimed in the present application.

Sequence Listing

6. The specification is objected to for referring to sequences without also identifying them by the sequence identifier assigned to them in the sequence listing as required by 37 CFR 1.821(d). See e.g., p ages 8-16, and 57 (referring to the disclosed consensus sequences without referring to them by their SEQ ID NO). The examiner would like to bring the applicant's attention to the following excerpt from MPEP §2422.03:

> 37 CFR 1.821(d) requires the use of the assigned sequence identifier in all instances where the description or claims of a patent application discuss sequences regardless of whether a given sequence is also embedded in the text of the description or claims of an application. This requirement is also intended to permit references, in both the description and claims, to sequences set forth in the "Sequence Listing" by the use of assigned sequence identifiers without repeating the sequence in the text of the description or claims. Sequence identifiers can also be used to discuss and/or claim parts or fragments of a properly presented sequence. For example, language such as "residues 14 to 243 of SEQ ID NO:23" is permissible and the fragment need not be separately presented in the "Sequence Listing." Where a sequence is embedded in the text of an application, it must be presented in a manner that complies with the requirements of the sequence rules.

The applicant is therefore required to amend the specification to comply with 37 CFR 1.821(d).

Claim Objections

7. Claims 32-44, 46, and 59 are objected to because of the following informalities: the claims refer to sequences in the application without identifying them by SEQ ID NO. It is suggested that the claims be amended such that the consensus sequences are referred to by SEQ ID NO, rather than by reference to the figures. See also, MPEP 2173.05(s) (stating "Incorporation by reference to a specific figure or table "is permitted only in exceptional circumstances where there is no practical way to define the invention in words and where it is more concise to incorporate by reference than duplicating a drawing or table into the claim.") In the present case, there is no necessity for referring to the figures in the claims as the claims may more easily refer to sequence identification numbers. Appropriate correction is required.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 32-37, 43, and 59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims read on genotype-specific peptides having amino acids deduced from domains in the disclosed HCV core proteins. It is not clear what the Applicant considers to be a genotype-specific domain. For example, the Applicant has indicated that the sequences comprising residues 67-78, 101-108, 144-155, and 157-63 of SEQ ID NO: 206 are genotype-specific domains. It is noted that, based on the alignment provided in Figure 7J, each of these sequences of SEQ ID NO: 206 varies from at least one of the other HCV core peptides disclosed in the figure. It therefore appears that a genotype-specific domain (or peptide) may include any domain that varies from the sequence of at least one other disclosed HCV core protein. However, on page 57 of the application, the Applicant has indicated that these same regions may not comprise genotype-specific peptides for other HCV core proteins despite their comprising sequence variations from the sequence of SEQ ID NO: 206. For example, the region comprising residues 157-163 of SEQ ID NO: 197 is not disclosed as an example of a genotype-specific domain despite the variations within this domain between SEQ ID NO: 197 with other sequences disclosed in Figure 7J. It is therefore unclear what is meant by a genotype-specific domain or peptide. It is unclear if such domains are determined based on the comparison of the core protein sequences to all other of the disclosed sequences, or if the determination of what domains constitute a genotype-specific sequence are based on comparison only to the disclosed consensus sequences. Clarification is required.

10. Claims 38-42, 44, 46, and 59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claim read on compositions comprising, and methods of using, a "universal peptide" from a universally conserved amino acid domain in the HCV core protein. It is not clear what is meant by a universal peptide or a universally conserved amino acid sequence as it is used in the present application. At first glance, the Applicant appears to be identifying as universal domains any domain that is conserved across all disclosed HCV core peptides. However, among the domains indicated by the Applicant is the domain of residues 93-108. Within this domain, there are several instances of variation within this domain. Cf., sequence of SEQ ID NO: 197, 205, and 206. Further, the same universal domain indicated above also comprises a domain indicated by the Applicant as a genotype-specific domain. See, App, page 57 (indicating that residues 101-108 of SEQ ID NO: 206 represent a genotype-specific domain). In view of this apparent inconsistency, it is unclear what is intended by the phrases "universal peptide" or "universally conserved domain." It is unclear what the precise definition of a universal peptide is intended to include in the present application. It is unclear if such peptides are limited to peptides that may be derived from the disclosed consensus sequences, if the peptides may include sequences in the indicated regions of any of the disclosed HCV core proteins, or if a universal peptide is intended to be a peptide sharing sequence identity with each of, or only a majority of, the disclosed HCV core proteins. Clarification of the claim language is required.

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 19 and 46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for immunogenic HCV compositions, does not reasonably provide enablement for anti-HCV vaccines comprising either SEQ ID NO: 206 or a fragment thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The Applicant has not provided an enabling disclosure for the use of the claimed polypeptides as a vaccine against HCV virus.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the courts have put forth a series of factors. See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988); and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Id. While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered.

The claim read on a vaccine composition comprising either SEQ ID NO: 206, or a "universal peptide" therefrom. In the immunological arts, a vaccine is understood to have some prophylactic or therapeutic effect. See e.g., definition of "vaccine" in either Stedman's Online

Medical Dictionary or The On-line Medical Dictionary. Thus, the claims read on prophylactic or therapeutic compositions comprising one of the indicated polypeptides.

While the claims are limited to a specific set of polypeptides, it is noted that the application has provided no examples or demonstration of HCV core antigens that were successful in inducing a therapeutic or prophylactic effect against HCV infection. Further, while the art indicates that the HCV core antigen may become an important part of an HCV vaccine, such a vaccine has yet, even after the filing of the present application, to be produced. See e.g., Isaguliants et al., Vaccine 22: 1656-65 (2004) (teaching that while the core protein has long been considered for making an HCV vaccine, those in the art have faced difficulties in the development of such a vaccine). See also, Zein et al., Microbes and Infection 4: 1237-46; and Koff, Int'l J Parasitol 33:517-23 (each teaching that those in the art have faced difficulties in the development of anti-HCV vaccines and that such vaccines are not presently available). Thus, the art demonstrates both unpredictability and complexity in the field of HCV vaccination. In view of these teachings in the art, and the lack of any effective examples of such vaccines in the application, the Applicant has not provided sufficient information to enable those in the art to make and use a vaccine comprising the claimed polypeptides.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 32-44, 46, and 59 are rejected under 35 U.S.C. 102(b) as being anticipated by DeLeyes et al. (EP 0 489 968 A). The claims read on genotype-specific and universal peptides of a HCV core protein selected from the Group of SEQ ID NOs: 155-206. DeLeyes teaches the use of HCV core protein peptides for the making of and the detection of anti-HCV antibodies. See, page 4 lines 15-19 (teaching the attachment of the peptides to carriers for the purpose of using the peptides to raising antibodies); and pages 5-6 (teaching methods of using the peptides for the detection of anti-HCV antibodies). Thus, the reference teaches the peptides, and methods of using them to detect HCV antibodies, and inherently, by virtue of teaching the use of the peptides to raise antibodies, teaches pharmaceutical compositions comprising the peptides. While the reference does not teach or suggest a vaccine comprising the peptides, there does not appear to be any structural distinction between the compositions indicated as useful for raising anti-HCV antibodies, and the vaccines of the present application.

On pages 3-4 of the reference, there is a list of several peptides that may be used in the disclosed compositions and methods. Examples of such peptides are the peptide indicated as peptide I, which appears to be a genotype-specific peptide for the protein of SEQ ID NO: 180 of the present application. Peptide II appears to be a universal peptide based on the consensus protein of Figure 7J of the present application. Peptide VI of the reference appears to teach a peptide comprising a having a genotype-specific sequence for the protein of SEQ ID NO: 160 of the present application. See, residues 9-20 of Peptide VI.

The reference therefore anticipates the indicated claims.

15. Claims 32, 37, 43, and 46 are rejected under 35 U.S.C. 102(a) as being anticipated by Shirai et al., J Virol 68(5): 3334-3342. These claims read on genotype-specific peptides from the HCV core protein, and pharmaceutically acceptable compositions comprising such peptides. For the purposes of this rejection, a genotype specific peptide is treated as a peptide derived from an HCV core peptide that varies from the sequence of a consensus sequence as disclosed in Figure 7 of the application.

The teachings of Shirai have been described in part above. In addition to the peptide described above, the reference also discloses a peptide referred to on page 3335 of the reference as peptide C8. This peptide shares identity with residues 140-156 of SEQ ID NO: 176 of the present application. In this region of the protein, SEQ ID NO: 176 varies by at least one residue from the consensus HCV core protein sequence. See, Figure 7J. The Shirai reference provides the same teachings regarding this peptide as were described with respect to the C7-P1oG peptide above. Shirai, pages 3335, and 3336. Shirai therefore anticipates the indicated claims.

16. Claims 38, 44, and 46 are rejected under 35 U.S.C. 102(a) as being anticipated by Shirai et al., J Virol 68(5): 3334-3342. These claims read on universal peptides from the HCV core protein, and pharmaceutically acceptable compositions comprising such peptides. Shirai discloses such peptides. See pages 3335, and 3336. The peptide disclosed as C7-P10G on page 3336 shares identity with residues 129-138 of SEQ ID NO: 206. These residues appear to comprise a universal peptide according to the claims. The reference further teaches the purification of the peptides, and their use for the in vitro sensitizing of T cells. Pages 3337

(abstract to Figure 2). Thus, the reference inherently teaches the combination of the peptides with a pharmaceutically acceptable carrier. Shirai therefore anticipates the indicated claims.

17. Claims 38-42, 44, 46, and 59 are rejected under 35 U.S.C. 102(b) as being anticipated by Ferroni et al., J Clin Microbiol 31(6): 1586-91. These claims read on universal peptides from SEQ ID NO: 206, and on methods of using such peptides for the detection of anti-HCV antibodies. On page 59 of the specification, the Applicant indicates several domains within the core protein that the Applicant considers to be universal peptides. Two such peptides are the peptides indicated as comprising residues 23-35 or residues 53-66 of the core protein. However, while the application indicates that these peptides are examples of universal peptides, the application indicates that these are examples of such peptides, and that the claimed universal peptides need not comprise these sequences.

Ferroni teaches the making and use of synthetic core protein peptides for the detection of HCV antibodies. Pages 1586-87. Two of the peptides disclosed (G15V and R15P) share identity along their length with the corresponding residues of SEQ ID NO: 206. One of these peptides falls within the domain of residues 23-35 identified above. The other overlaps with the regions indicated as comprising residues 53-66. Thus, the reference anticipates claims 38-42. Further, because the peptides of the reference appear to be universal peptides, and because antibodies that bind such peptides would inherently be capable of binding to epitopes of other HCV core proteins from other HCV isolates, the reference also anticipates claim 59.

Claims 44 and 46 further read on pharmaceutical compositions comprising the indicated peptides. On page 1586, the reference indicates that the peptides are diluted in a sodium

carbonate buffer prior to adsorption to plates for running the ELISA assays. Sodium carbonate is recognized in the art as a pharmaceutically acceptable buffer. See e.g., U.S. Patent 5,298,410, column 5 lines 20-30. Thus, the reference teaches the compositions of claim 44 and 46. While the reference does not disclose the use of the peptides as a vaccine as indicated in claim 46, the intended use of claim 46 does not structurally distinguish the claim from the composition disclosed by the reference.

18. Claims 32-37, 43, and 46 are rejected under 35 U.S.C. 102(b) as being anticipated by Machida et al., Hepatology 16: 886-91 (of record in the May 1998 IDS). The claims have been described above. Machida teaches peptides and methods of using peptides for the detection of HCV antibodies corresponding to residues 34-81 of the sequences disclosed in Figure 7A-1 of the present application. The reference therefore anticipates the indicated claims.

Claim Rejections - 35 USC § 103

19. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

20. Claims 4 and 5 are rejected under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over the teachings of Li et al., Biochem Biophys Res Comm 199(3): 1474-81 (of record in the IDS of May 26, 1998); or of Takeuchi et al., J Gen

Virol 71: 3027-33 (of record in the May 1998 IDS). These claims read on an isolated protein encoded by the DNA of one of SEQ ID NOs: 103-154, or comprising the amino acid sequence of one of SEQ ID NOs: 155-206; each sequence of which either encodes or comprises an HCV core protein sequence.

Li teaches the DNA and core protein sequences of several HCV isolates. Page 1480, Figure 3. One of these sequences, that of the F1-H isolate, is identical to the sequences indicated for SEQ ID NOs: 156-160 in Figure 7A of the present application. Takeguchi teaches a HCV core protein with the sequence of SEQ ID NO: 166 of the present application in a like manner. Because the references teach claimed sequences, the teachings either anticipate, or render obvious the claimed invention.

21. Claims 4, 5, 11-15, 16, and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over either of Takeuchi or Li as applied to claims 3 and 4 above, and further in view of Liao et al., U.S. Patent 5,645,983. These claims read on methods of detecting anti-HCV using, and on immunogenic compositions comprising, a core protein of HCV. The teachings of Li have been described above. Liao teaches the use of a CV core protein for the detection and production of anti-HCV antibodies. However, the reference does not teach one of the HVC core proteins indicated in claims 4 or 5.

However, in view of the teachings of Liao, it would have also been obvious to those in the art to substitute the HCV core protein in Liao for the protein disclosed by Li or Takeguchi as each were recognized in the art as HCV core proteins. The combination of Li or Takeguchi and Liao therefore render the indicated claims obvious.

22. Claims 32-37, 43, and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li as applied to claims 3 and 4 above, and further in view of Chien et al., U.S. Patent 6,054,264. These claims have been described above, as have the teachings of Li. Chien teaches the use of type-specific epitope of an HCV core protein for the production and detection of type-specific anti-HCV antibodies. See, column 2, and cols 6-8 (esp col. 7 lines 31-37). Chien does not, however, appear to teach epitopes from the sequences disclosed in the present application. However, from the teachings of Chien, it would have been obvious to derive peptides such as those in Chien from the HCV core proteins disclosed in Li. It would also have been obvious to use such peptides for the same purposes as disclosed in Chien. The combination of these references therefore renders the claimed inventions obvious.

Conclusion

23. No claims are allowed. However, SEQ ID NO: 206, and peptides comprising the sequences of one or more of residues 67-78, 101-108, 144-155, or 157-163 of SEQ ID NO: 206 appear to be free of the prior art.

24. The following prior art references are made of record and considered pertinent to applicant's disclosure. However, while relevant they are also not used as a basis for rejection for the stated reasons.

> Wang, U.S. Patent 5,436,126; and Wands et al., U.S. Patent 4,870,026. These references are considered relevant to the claimed inventions. However, the teachings of these references are considered redundant to those of the documents cited above.

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 571-272-0905. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Z. Lucas
Patent Examiner

5/17/04

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